Case reports

Commentary: "Histiocytosis X"

Dinah V Parums

Pulmonary Langerhans' cell granulomatosis (LCG) is a diffuse, smoking-related lung disease characterised pathologically by bronchiolocentric inflammation, cyst formation, and widespread vascular abnormalities, and physiologically by exercise limitation. Pulmonary fibrosis is a long term sequel. Diagnosis may be made by lung biopsy and by bronchoalveolar lavage (BAL).

The papers by Gabbay *et al*[1] and Habib *et al*[2] present two cases of LCG which recurred after double lung transplantation at two years and four years, respectively. These are the first reports of recurrent LCG in the transplanted lung. As lung transplantation is now recognised as a treatment for this disease, these two reports serve to draw our attention to what may prove to be the beginning of a series of such cases.

The titles of these two papers[1 2] also draw our attention to the remaining confusion about the terminology of this disease. This confusion has been based upon historical morphological reports. The "histiocytoses" are reactive or proliferative diseases of cells of the mononuclear phagocyte system classically seen in childhood, and they include Langerhans' cell histiocytosis (LCH) or granulomatosis (LCG), haemophagocytic syndrome (familial and reactive), sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), juvenile xanthogranuloma, and malignant histiocytosis. These disorders show wide variation in their clinical presentation, prognosis, and genetic implications.[3] All are characterised by localised or generalised proliferation of histiocytes, but they differ in their morphology, histochemical and immunochemical staining patterns, and electron microscopical features. Histiocytic diseases may be generalised or involve single organs with involvement of the bone, skin, spleen, brain and lung, in order of frequency.[4 5]

The term "histiocytosis X" was meant to cover a spectrum of three diseases: eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. However, these terms are rather meaningless pathologically. Hand-Schüller-Christian disease has become a synonym for multifocal LCG. The term Langerhans' cell histiocytosis (LCH)[2] reflects the belief that this disease is a true "histiocytosis". Some prefer the term Langerhans' cell granulomatosis (LCG)[1] to avoid confusion with the term histiocytosis X because there is some evidence to support the view that the Langerhans' cell is not a member of the mononuclear phagocyte system and hence not a tissue macrophage (or histiocyte).[3 5]

Langerhans' cells are part of the widespread system of "dendritic cells" which arise from CD34+ progenitors in the bone marrow. Langerhans' cells are specialised and efficient antigen presenting cells for T cell mediated immunity. In LCG, however, the major associated cells are not T cells but mature eosinophils, hence the original name "eosinophilic granuloma".

These two case reports have elegantly demonstrated the role of immunohistochemistry in confirming the diagnosis and have relied upon the use of S100 as a marker for the Langerhans' cell. The immunophenotype and proliferation fraction have been investigated recently in 26 cases of LCG.[3] In all cases LCG cells were positive for S100 protein, CD1a, or both. In most cases LCG cells expressed the macrophage associated marker CD68 and, in two cases, they contained lysozyme. Expression of both cytoplasmic CD2 and CD3 was observed in cryostat sections. An unexpected finding was the presence of placental alkaline phosphatase in LCG cells. Langerhans' cells in normal skin were negative for both CD2 and CD3, but a proportion contained placental alkaline phosphatase.

Langerhans' cell granulomatosis has been regarded as a non-malignant, reactive condition, implying that the DNA content of the Langerhans' cells is normal. However, Isaacson *et al*[5] have recently shown that LCG cells have an aberrant phenotype and are proliferating locally. Mitoses are seen in the Langerhans' cells in LCG which might suggest that LCG is a neoplastic rather than a reactive process. The implications of these studies may be of relevance in determining future treatment regimes.

Subjects with pulmonary LCG present with either normal or predominantly restrictive pulmonary physiology; exercise impairment is common and appears to reflect pulmonary vascular dysfunction.[6] The course of pulmonary LCG is variable, difficult to predict, and ranges from spontaneous remission to progressive respiratory insufficiency and death. To identify the determinants of survival Delobbe *et al*[4] recently performed a survival analysis on 45 patients with pulmonary LCG. The patients were aged from 12 to 62 years, 32 were men, and they were almost exclusively current smokers (96%). These 45 patients were followed for a median period of six years (range 1–29) after the diagnosis. During the period of observation 33 patients (73%) survived (median follow up period 5.8 years; range 1–29) and 12 (27%) died or underwent lung

Department of Histopathology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
D V Parums

Correspondence to:
Dr D V Parums.

transplantation (median follow up 8.4 years; range 1.4–16.1). The median survival was approximately 13 years. A univariate analysis showed that diminished survival was significantly associated with an older age at diagnosis, a lower forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio at diagnosis, a higher residual volume/total lung volume (RV/TLV) ratio at diagnosis, and steroid therapy during follow up.

Recurrent LCG may mimic obliterative bronchiolitis (OB) in the transplanted lung. The bronchiolocentricity of the disease and the association with smoking suggest that there is an immunological basis to the genesis or the progression of the disease, so the first line of treatment is for the patient to stop smoking. The involvement of Langerhans' cells in T lymphocyte mediated immune reactions raises the possibility of a role for transplant immunosuppressive therapy including cyclosporin and prednisolone in the treatment of recurrent LCG.[7] As the case report by Gabbay *et al*[1] has shown, cyclophosphamide may prove to be effective in the treatment of recurrent pulmonary LCG.

In conclusion, these two reports have shown that it is important to think of the possibility of the diagnosis of recurrent pulmonary LCG in lung transplant patients and that this disease can mimic bronchiolitis obliterans syndrome clinically. Adequate tissue for histopathological examination and the use of immunophenotypic markers will confirm the diagnosis. Clinical trials are now awaited to determine appropriate treatment regimes for recurrent LCG in the context of the transplanted lung.

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Recurrence of recipient Langerhans' cell histiocytosis following bilateral lung transplantation

S B Habib, J Congleton, D Carr, J Partridge, B Corrin, D M Geddes, N Banner, M Yacoub, M Burke

Transplant Unit, Harefield Hospital, Harefield, Middlesex UB9 6JH, UK
S B Habib
J Partridge
N Banner
M Yacoub
M Burke

Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
J Congleton
D Carr
B Corrin
D M Geddes

National Heart and Lung Institute of Imperial College of Science Technology and Medicine, University of London, Dovehouse Street, London SW3 6LY, UK
B Corrin
N Banner
M Yacoub

Correspondence to:
Dr M Burke, Department of Pathology, Harefield Hospital, Harefield, Middlesex UB9 6JH, UK.

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Abstract

Langerhans' cell histiocytosis may cause irreversible respiratory failure due to progressive destruction of lung parenchyma and widespread cystic change. Transplantation offers a therapeutic option. A case is described of recurrence of Langerhans' cell histiocytosis which was associated with deterioration in lung function four years following bilateral lung transplantation. Patients transplanted for Langerhans' cell histiocytosis should be followed up with this complication in mind.
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Keywords: Langerhans' cell histiocytosis; lung transplantation; recurrence

Case report

An otherwise fit 27 year old Asian male martial arts instructor presented in mid 1991 with recurrent spontaneous pneumothorax. He smoked 10 cigarettes per day and was taking no medication. A diagnosis of pulmonary Langerhans' cell histiocytosis was made based on the clinical picture and on the radiological findings. Chest radiography and high resolution computed tomographic scanning showed reticular shadowing and widespread cystic changes in the lower lobes. A lung biopsy specimen showed reactive pleuritis and interstitial emphysema but no evidence of active or burnt out Langerhans' cell histiocytosis. The skull radiograph was normal and a bone scan showed non-specific changes.

Lung function deteriorated over the next two years, with reduction in forced expiratory volume in one second (FEV_1) to 0.88 litres (22% predicted) and of forced vital capacity (FVC) to 2.04 litres (44% predicted). In April 1993 he underwent double lung transplantation with internal mammary artery revascularisation. The diagnosis of Langerhans' cell histiocytosis was confirmed on histological examination of the explanted lungs, showing florid active disease as well as cystic change consistent with burnt out Langerhans' cell histiocytosis. The active lesions consisted of collections of non-pigmented mitotically active Langerhans' cells interspersed with eosinophils and lymphocytes.

Postoperative recovery was complicated by pneumonia due to *Pseudomonas aeruginosa* and cytomegalovirus pneumonitis, both conditions responding to appropriate therapy. Immunosuppression consisted of cyclosporin and azathioprine with initial oral prednisolone which was slowly withdrawn over the first year. At his first annual assessment he was clinically stable. Selected mammary artery angiography showed